



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 20 2012

Milan M. Vinnola
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RE: Request for Revision of Regulatory Review Period, Kepivance
Docket No. FDA-2005-E-0310¹

Dear Ms. Vinnola:

This letter is in response to the May 24, 2007, request on behalf of Novartis Vaccines and Diagnostics, Inc. (Novartis), for reconsideration and revision of the regulatory review period for Kepivance (palifermin), U.S. Patent No. 5,677,278, filed by Chiron Corporation (Chiron), now Novartis, under 35 U.S.C. 156 et seq. In the *Federal Register* of April 2, 2007 (72 FR 15699), the Food and Drug Administration (FDA) published its determination of this product's regulatory review period for purposes of patent term extension, as required under 35 U.S.C. 156(d)(2)(A). As described below, FDA affirms the determination of the regulatory review period as published.²

I. YOUR REQUEST

You believe the date FDA published in the *Federal Register* and determined as the date the Kepivance application was initially submitted — June 15, 2004 — is incorrect, and you request a revision of the date to May 14, 2004, and recalculation of the regulatory review period for the “fast track product.” You provide the following assertions in support of your request:

- The biologics license application (BLA) for Kepivance was submitted under section 351 of the PHS Act and was reviewed by FDA as part of its fast track program. The BLA was submitted in two reviewable units. Reviewable Unit 1 of the BLA was submitted to FDA on May 14, 2004, and Reviewable Unit 2 of the BLA was submitted to FDA on June 15, 2004.
- The date the marketing application was “initially submitted” for purposes of determining the length of patent term extension should be May 14, 2004, when the first reviewable unit was submitted to FDA. To the extent that FDA considers the term “initial submission” within the meaning of 35 U.S.C. 156(g)(1)(B) ambiguous, FDA

¹ This request was originally assigned docket number 2005E-0245. The number was changed to FDA-2005-E-0310 as a result of FDA's transition to its new docketing system (www.regulations.gov) in January 2008.

² Please note: A technical correction of the *Federal Register* notice “Determination of Regulatory Review Period for Purposes of Patent Extension; KEPIVANCE” (72 FR 15699) will be published to correct the statute under which the Kepivance application was submitted (section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) rather than section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355)).

should reconsider its interpretation in the context of "fast track" submissions. It is reasonable for FDA to interpret the date the marketing application was "initially submitted" as the date the first reviewable unit is submitted for purposes of patent term extension, but to also conclude the application was not submitted for purposes of starting the review clock until after all of the reviewable units necessary for a complete review are submitted.

- Under section 736(a)(1)(B) of the FD&C Act (21 U.S.C. 379h(a)(1)(B)), user fees "shall be due upon submission of the application or supplement." FDA has no authority to require that fees be paid before submission of the application.
- FDA requested and Amgen (Chiron's licensee) paid the full BLA user fee at the time of the May 14, 2004, submission.
- FDA's request for payment under section 506(c)(1)(B) of the FD&C Act (21 U.S.C. 356(c)(1)(B)) is evidence of Congressional intent that the initial reviewable unit would be a "submission" under the law. That section of the law says that FDA will commence review of an advance submission only after the applicant pays any fee that may be required under section 736. No fee is required under section 736 except "upon submission" of the BLA.
- Section 506(c)(1)(B) of the FD&C Act is evidence that Congress understood that the initial reviewable unit of a fast track product would be a "submission" under the statute. The statute says, "if the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application."

You ask that FDA reconsider its interpretation of the date a marketing application is "initially submitted" in the context of fast track submissions. You state that the BLA submission date marks the termination of the IND testing phase of the development of the drug and begins the phase during which FDA commences review of the data developed during the testing phase. You further argue that the BLA initial submission date should correspond with the date of submission of the first reviewable unit of the BLA. You believe that records of teleconferences with FDA underscore that the first reviewable unit of the BLA submitted on May 14, 2004, contained sufficient information to allow FDA to commence review and that FDA had initiated review prior to the submission of the second reviewable unit.

II. BACKGROUND

A. Applicable Statutory Provisions

With respect to regulatory review periods, 35 U.S.C. 156(g) provides as follows.

For purposes of this section, the term "regulatory review period" has the following meanings:

(1)(B) The regulatory review period for a new drug, antibiotic drug, or human biological product is the sum of--

- (i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505, or 507, and
- (ii) the period beginning on the date the application was initially submitted for the approved product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section.

Under section 506(c) of the FD&C Act — Review of Incomplete Applications for Approval of a Fast Track Product:

- (1) In general, if the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application. The Secretary shall commence such review only if the applicant —
 - (A) provides a schedule for submission of information necessary to make the application complete; and
 - (B) pays any fee that may be required under section 736.

- (2) EXCEPTION.—Any time period for review of human drug applications that has been agreed to by the Secretary and that has been set forth in goals identified in letters of the Secretary (relating to the use of fees collected under section 736 to expedite the drug development process and the review of human drug applications) shall not apply to an application submitted under paragraph (1) *until the date on which the application is complete* (emphasis added).

B. Marketing Application

In the patent term restoration regulations in Title 21 Code of Federal Regulations (21 CFR) part 60, a *marketing application* for patent term extension purposes is defined in section 60.3(b)(12) to mean an application for:

- (i) Human drug products submitted under section 505(b) of the [FD&C] Act or section 351 of the PHS Act; . . .

Section 601.2(a) (21 CFR 601.2(a)) of the biologics licensing regulations states:

To obtain a biologics license under section 351 of the [PHS] Act for any biological product, the manufacturer shall submit an application to the Director. . . on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency; . . . a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s); . . . specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide. . . ; and the address of each location involved in the manufacture of the biological product. . . The applicant shall also include a financial certification or disclosure statements or both for clinical investigators. . . .

An application for a biologics license shall not be considered as filed until all pertinent information and data have been received by the Food and Drug Administration. . . .

C. Regulatory Review Period for Patent Term Extension Purposes

For purposes of patent term extension, a regulatory review period is the sum of two periods of time: a testing phase and an approval phase. As clarified in 21 CFR 60.22(a)(1), for human drug products, the testing phase begins on the date an exemption under section 505(i) of the FD&C Act becomes effective for the approved human drug product and ends on the date a marketing application under section 351 of the PHS Act or section 505 of the FD&C Act is initially submitted to FDA. Section 60.22(a)(2) generally tracks the statutory language and states that

[t]he approval phase begins on the date a marketing application under section 351 of the [PHS] Act or section 505(b) of the [FD&C] Act is initially submitted to FDA . . . and ends on the date the application is approved.

Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a biologic product will include all of the testing phase and approval phase, as specified in 35 U.S.C. 156(g)(1)(B).

III. DISCUSSION

A. What is the initially submitted date for the Kepivance BLA?

While it may be reasonable to view the receipt by FDA of the first reviewable unit of the BLA as a "submission," we disagree with your conclusion that this submission meets the standard for the submission of *an application* within the meaning of the applicable statutory and regulatory

authorities regarding regulatory review periods. FDA interprets these authorities to mean that the approval phase, as described above, commences when the Agency receives a *complete* application, not when it receives a submission containing the first partial unit of such an application.

According to 21 CFR 60.3(b)(12)(i), for patent term restoration purposes, a marketing application means an application for human drug products submitted under section 505(b) of the FD&C Act or section 351 of the PHS Act. As noted in the legislative history of the Drug Price Competition and Patent Term Restoration Act of 1984:

[F]or purposes of determining the regulatory review period and its component periods, an application for agency review is considered to be "initially submitted" if the applicant has made a deliberate effort to submit an *application containing all information necessary* (emphasis added) for agency review to begin. The legislative committee recognizes that the agency receiving the application might decide it needs additional information or other changes in the application. As long as the application was complete enough so that agency *action* (emphasis added) could be commenced, it would be considered to be "initially submitted."³

As noted in section II.B, a marketing application may contain a number of different components. It is FDA's position that for the purposes of patent term extension, a marketing application is considered to be "initially submitted" when the agency has *all* the elements required by statute and regulation to make an approval decision. The legislative record, cited above, is consistent with this interpretation — it is more than reasonable to infer that where Congress refers to a submission that is "complete enough" to allow "agency action," it meant to describe a document containing all the information required for marketing approval under the applicable statutory and regulatory authorities. Nothing in the legislative history suggests that the mere submission of partial testing data can trigger the approval phase. The last sentence in the above quotation merely states the common understanding that once the sponsor submits a complete application containing all the required information, that application would still be considered "initially submitted" even if FDA later decided to request additional information, such that minor amendments or changes made to such an application would not "reset" the clock for the beginning of the approval phase. This interpretation is also consistent with section 506(c)(2) of the FD&C Act, which states that the time period for review of an application does not start until the date on which the application is complete.

FDA's guidance for industry on *Fast Track Drug Development Programs — Designation, Development, and Application Review* (Fast Track Guidance)⁴ states that FDA will only accept portions of an application eligible for early submission if that section submitted for review will be in a form adequate to have been included in a complete BLA or NDA submission.⁵ It also

³ H. Report No. 98-857, part 1, June 21, 1984.

⁴ Available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf>.

⁵ Fast Track Guidance at 13.

states that acceptance of a portion of an application by the Agency does not necessarily mean that review will commence or proceed prior to the receipt of a complete application. Under the Fast Track Guidance, a request for fast track designation may be made by a sponsor “at the time of original submission of its IND, or at any time thereafter prior to receiving marketing approval of its BLA or NDA.”⁶ This time frame includes the time *after* a complete application has been submitted to FDA. The Fast Track Guidance also makes it clear that “[t]he review clock will not begin until the applicant informs the Agency that a complete BLA or NDA has been submitted.”⁷ Taken together, these provisions support the Agency’s interpretation that a BLA or NDA, including those that are submitted as fast track applications, is considered to be initially submitted when the Agency receives a complete application.

FDA’s interpretation of the phrase “initial submission” has been upheld by courts⁸ within the context of patent term extension for new animal drugs, where Congress used the identical phrase (“initially submitted”) to describe when the approval phase begins for such products.⁹ Wyeth, which had taken advantage of FDA’s “phased review” policy concerning new animal drug applications (NADAs) to submit portions of its application in stages, argued that statute should be interpreted to mean that its NADA was “initially submitted” when it submitted the first technical section. FDA, on the other hand, asserted that “the date that it may commence review of individual technical sections is irrelevant. . . . [F]or purposes of 35 U.S.C. § 156(g), what matters is the date that FDA may commence review of a [complete] application.”¹⁰ The Federal Circuit held that “the plain language [of 35 U.S.C. 156(g)] does not clearly indicate when an application is initially submitted”¹¹ and that FDA’s interpretation of “initial submission” to mean a complete application was permissible.¹² Finally, although the issue in *Wyeth* arose under a separate program involving slightly different regulatory procedures, the court also noted that FDA’s interpretation of “initial submission” in the context of new animal drug applications was not inconsistent with the Agency’s interpretation of the same phrase in the context of new human drug applications.¹³

Although the first reviewable unit of the BLA for Kepivance, a fast track designated product, included some of the technical sections of an application that were complete for the particular discipline component as recommended in the Fast Track Guidance and was allowed to be submitted for potential Agency review under section 506(c) of the FD&C Act, it was not a complete marketing application containing all the required elements that would enable Agency

⁶ *Id.* at 8.

⁷ *Id.* at 14. We decline your invitation to interpret what constitutes a complete application differently for purposes of starting the review clock than for the purposes of patent term extension because you have not supplied reasonable grounds for doing so.

⁸ See *Wyeth Holdings Corp. v. Sebelius*, 603 F.3d 1291 (2010).

⁹ New animal drug patent term extension provisions in 35 U.S.C. 156(g)(4)(B)(ii) provide that the approval review period for such products is: “the period beginning on the date the application was *initially submitted* for the approved animal drug product under subsection (b) of section 512 and ending on the date such application was approved under such section.” (Emphasis added).

¹⁰ *Wyeth*, *supra* note 8, at 1297.

¹¹ *Id.*

¹² *Id.* at 1330.

¹³ *Id.*

action. According to FDA records, the clinical data section and the pharmacology data section — key components of a complete marketing application — were not submitted until June 15, 2004, when the second reviewable unit of the BLA arrived at FDA. These key components are required in a *complete* marketing application for FDA to make a decision regarding approval.

Accordingly, we affirm our determination that the date the Kepivance application was “initially submitted” for purposes of determining the end of the testing phase and the beginning of the approval phase is June 15, 2004, when the marketing application was complete (i.e., when it contained all the information necessary for the Agency to make an approval decision).

B. Can FDA require that user fees be paid before submission of an application?

Section 736(a)(1)(B) of the FD&C Act states that “the fee required by section 736(a)(1)(A)¹⁴ shall be due upon submission of the application or supplement.” You believe that FDA has no authority to require that application user fees be paid before submission of the application and you stress that FDA requested payment of the full BLA user fee at the time of submission of the first reviewable unit on May 14, 2004. You conclude that because the fee was required upon a partial submission under section 736 of the FD&C Act, the May 14, 2004, receipt date of the initial reviewable unit of the BLA should be the date of initial submission of the BLA.

Section 506 of the FD&C Act, Fast Track Products, is intended to facilitate the development of fast track products and to expedite the review of fast track products for the treatment of serious or life-threatening conditions. As stated in section 506(c) of the FD&C Act, Review of Incomplete Applications for Approval of a Fast Track Product, FDA may evaluate for filing, and may, at its discretion, commence review of portions of an application for the approval of the product before the sponsor submits a complete application, but “only if the applicant (A) provides the schedule for submissions to make the application complete; and (B) *pays any application fee that may be required under section 736 [of the FD&C Act]*” (emphasis added).

This statutory provision indicates that Congress intended that FDA be provided with resources to devote to fast track product development by requiring payment of any human drug application fees with the submission of an *incomplete* marketing application under this section. In these cases, for a fast track product, FDA does have the authority to require the payment of a fee under section 736 of the FD&C Act before it receives a complete application. However, receipt of such payment does not turn an incomplete submission into a complete submission for purposes of determining the regulatory review period. As section 506(c)(2) makes clear, although FDA may, at its discretion, begin reviewing portions of an application before it is complete, the official time period for the review of an application that is submitted in stages under section 506(c)(1) does not begin to run “until the date on which the application is complete.”

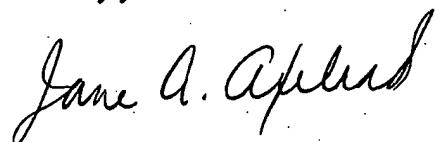
¹⁴ Human Drug Application and Supplement Fee (21 U.S.C. 379h(a)(1)).

IV. CONCLUSION

FDA has reviewed its records and your request for reconsideration and revision of the regulatory review period for Kepivance, U.S. Patent No. 5,677,278, under 35 U.S.C. 156 et seq. published in the *Federal Register* of April 2, 2007. FDA denies your request to adjust the initially submitted date of the Kepivance BLA from June 15, 2004, the date the complete marketing application was received, to May 14, 2004, the date of submission of the first reviewable unit containing only portions of the application. FDA affirms the determination of the regulatory review period as previously published.¹⁵

Please let me know if we can be of further assistance.

Sincerely yours



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research.

¹⁵ Including a technical correction of the *Federal Register* notice as described in note 1.